

In the Claims (clean copy as amended)

- a<sup>1</sup>
1. A process for isolating an intact clone of one target nucleic acid fragment having a known characteristic, from a number of fragments, said method being useful to isolate an intact nucleic acid fragment and diagnose genetic disease, comprising:
    - a) preparing an initial library of clones from said number of fragments using a vector containing no more than a pre-determined number of known restriction sites;
    - b) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries;
    - c) screening said group of monodigested libraries for said known characteristic to detect the presence of intact target fragments, to thereby determine those restriction enzymes to which said target fragment is insensitive;
    - d) subjecting said initial library to substantially all of said plurality of restriction enzymes to which said target fragment is insensitive, to produce a multidigested library having an intact clone of the target nucleic acid fragment; and
    - e) isolating an intact clone from the multidigested library.
  2. The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 10 restriction enzymes.
  3. The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 50 restriction enzymes.
  4. The process of Claim 1 wherein said plurality of restriction enzymes comprises at least 70 restriction enzymes.

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5. The process of Claim 1 wherein said pre-determined number of known restriction sites is four.

6. The process of Claim 1 wherein said pre-determined number of known restriction sites is three.

7. The process of Claim 6 wherein at least one of said three sites is different from, and flanked by, said two remaining sites.

9. The process of Claim 1 including the further step of transforming and replicating said intact clone of the target nucleic acid fragment.

10. The process of Claim 9 including the further step of isolating said intact clone.

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12. The process of Claim 1 comprising, after step b), the further step of transfecting said monodigested libraries in cellular hosts.

13. The process of Claim 1 comprising the further step of verifying the presence of said target fragment in said initial library by transfecting in a cellular host and screening said transfected host for the presence of said target fragment.

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14. The process of Claim 1 comprising the further step of verifying the presence of said target fragment in said multi-digested library by transforming said library and screening said transformed library for the presence of said target fragment.

15. The process of Claim 1 wherein said number of fragments contains up to  $10^8$  fragments, each from about 0.1kb to 5kb in size.

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16. A process for isolating an intact clone of one target nucleic acid fragment having a known characteristic, from a group of fragments, said method being useful to isolate an intact nucleic acid fragment and diagnose genetic disease, comprising:

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- a) preparing an initial library of clones from said number of fragments using a vector containing no more than a pre-determined number of known restriction sites;
  - b) verifying the presence of said target fragment in said initial library by transfecting in a cellular host and screening said transfected host for the presence of said target fragment;
  - c) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries;
  - d) independently transfecting said monodigested libraries;
  - e) screening said group of monodigested libraries for said known characteristic to detect the presence of intact target fragments, to thereby determine those restriction enzymes to which said target fragment is insensitive;
  - f) subjecting said initial library to substantially all of said plurality of restriction enzymes to which said target fragment is insensitive, to produce a multidigested library having an intact clone of the target nucleic acid fragment; and
  - g) transforming said multidigested library.
- sub contd

17. The process of Claim 16 wherein said restriction enzymes have cleavage sites from 5 nucleotides in length.

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19. A method for producing a series of monodigested libraries from a group of fragments, said method comprising:

- a) preparing and initial library of clones from said group of fragments using a vector containing no more than a pre-determined number of known restriction sites;

*3*  
*with*  
and

b) subjecting said initial library to a plurality of restriction enzymes individually, which plurality of enzymes do not include those to which said vector is sensitive, to produce a group of monodigested libraries.

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*24*  
21. The isolated intact clone of the target nucleic acid fragment of Claim 1.

22. A process of identifying or characterizing the clone of Claim 21, said process comprising cleaving, purifying, and sequencing the clone.

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